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Study protocol for an online randomized controlled trial among non-treatment seeking problem gamblers: training inhibition in online problem gambling (TRAIN-online) trial

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Abstract

Introduction Gambling disorder represents a major challenge in public health, with considerable individual and social burdens and high treatment gap. Fully Internet-based randomized controlled trial could be particularly relevant and acceptable in gambling disorder. In this project, we will aim to assess the efficacy of a web-based intervention of cognitive training of inhibition, among problem gamblers.

Methods and Analysis This will be a single blinding, randomized, comparative therapeutic web-based, controlled trial. Up to 200 adult problem gamblers with a Problem Gambling Severity Index-recent (PGSI-recent) score ≥5 will be included. The intervention will be a computerized cognitive training program targeting inhibitory skills. The comparator will be a computerized neutral sensorial program. Both programs will be carried out under similar conditions: biweekly online training for 6 weeks and telephone support will be offered to patients regarding their convenience for exercises debriefing. The main objective of the study is to assess the clinical efficacy of the online cognitive training program at 6 weeks, measured with the PGSI-recent. The secondary objectives of the study are to assess the efficacy on the gambling behavior assessed by the account-based gambling data, on the self-reported gambling practice, and on the inhibition performance at the neuropsychological level at 6, 14 and 52 weeks. We will also assess the acceptability of this program and the preferred level of guidance of the non-treatment seeking problem gamblers. Data analysis will be in intention-to-treat.

Ethics and dissemination This RCT will be executed in compliance with the Helsinki Declaration, and was approved by the CPP in October 2017. The findings will be published in peer-reviewed journals.

Trial registration number NCT03673800

Strengths and weaknesses of this study:

- This study assesses the clinical efficacy of an innovating web-based intervention of cognitive training in problem gambling.
- Efficacy is documented from different perspectives: clinical ones, i.e. subjective patient-reported outcomes and objective account-based gambling data, and neuropsychological assessments.
- An optional guidance by phone performed by a trained neuropsychologist is proposed and focuses on the transferability of the tasks in the patient real life.

- Completion of an online neuropsychological assessment (with the SST task) with no face to face is a challenge and limits the interpretation of the participant cognitive abilities.

INTRODUCTION

Gambling disorder represents a major challenge in public health, with a human and social considerable burden. Despite guidelines for responsible gambling standards[1], online problem and pathological gambling is an increasing challenge to healthcare providers because of its significantly increasing prevalence.[2-4] Online gambling may be more likely to contribute to problem gambling than offline environments.[5] Treatment gap is concerning: according to the ODJ national survey[6], only 2% of French problem gamblers seek medical care. Self-stigma and unawareness of professional sources of help have been described as barriers to accessing the healthcare system in those with gambling disorder.[7] Targeted online interventions among the most at-risk online gamblers could enhance the efficacy of the existing strategies and enlarge the range of existing sources of help.[8] No medication is currently approved for the treatment of gambling disorder. Therapeutic interventions still have a demonstrated limited effect size in published trials.[9] The more established interventions are motivational ones, cognitive behavioral therapies (CBT), or a combination of both techniques.[10] In this project, we will propose an alternative intervention of cognitive training among problem gamblers.

Cognitive training is an operationalized type of cognitive remediation. It is currently used to improve neuropsychological functioning in reason of its supposed malleability and its relation to daily activities.[11] Indeed, the purpose of these kind of training is to obtain transfer to ecological situations that is to say beyond experimental practices and in a real-life perspective.[12-13] Several studies supported the possibility of generalization of skills trained during cognitive rehabilitation programs after the sessions as it has been shown in psychiatric disorders, such as schizophrenia[14]. Cognitive training is currently used in several neuropsychiatric conditions,[15-17] but very few cognitive training programs have been published and tested in addictive disorders.[18] Content of assessed programs was heterogeneous, and usually targeted multiple executive functions: attention, working memory and spatial orientation[19-21], visual-motor coordination, and visual-spatial skills.[22] Most of them reported direct neuropsychological outcomes, while some of them could show parallel evolution in non-strictly cognitive outcomes, i.e. well-being and craving.[21-23] Cognitive training as a therapeutic tool for cognitive control impairments has been documented in conditions such as attention-deficit hyperactivity disorder (ADHD) or schizophrenia,[24] for instance by four consecutive days of training on a behavioral inhibition task (stop signal task (SST)).

Despite the robust data documenting the inhibition deficit in addictive disorder, very few data are available on the efficacy of cognitive training tasks or programs targeting inhibition skills.

However, Nora Volkow and her team (2015) supported the therapeutic potential in addiction, including gambling disorder, of interventions that improve self-regulation skills.[25] The most explored lead is cognitive bias modification and cue-specific motor response inhibition.[23] However, practicing a non-specific task of self-control (i.e. avoiding sweets and tightening a handgrip) could prevent relapse in smokers.[26] Noel et al. showed a significant effect of an inhibition task on decision making in patients with alcohol use disorder and problem gamblers.[27] Interestingly, the tasks assessed were not specifically designed for a substance or a behavior. That means that training on a task that does not refer to any substance or to any addictive behavior could improve addiction symptoms. It would imply transferability of the enhanced skills to daily life and other contexts as a general process in the psychopathological outcomes. From a transdiagnostic point of view inhibitory control is a core vulnerable process of substance and behavioral addictions[28] which could be thus trained with durable effects in both treatment and prevention of addiction as well as in daily life activities. In a recent study, Penolazzi et al. tested the transdiagnostic hypothesis of inhibitory control deficits in gambling disorders.[29] The results show preserved memory inhibition and impaired motor response inhibition, a pattern of deficits opposite to that previously reported for substance used disorders. These findings suggest that cognitive training targeting motor and visuospatial inhibitory control could be more adapted to online gamblers.

Fully Internet-based randomized controlled trial is an emerging design that could be particularly relevant and acceptable in this population, for whom the Internet is the medium of addictive behavior.[30] One recent study has shown no between-group difference with placebo of fully online cognitive behavioral therapy among non-treatment seeking problem gamblers.[31] We propose a web-based, randomized, controlled, single-blinding clinical trial, assessing the efficacy of cognitive training program targeting inhibition, in patients with problem gambling.

Aims and objectives

Primary objective

The main objective of the study is to assess the clinical efficacy of an online computerized cognitive training program targeted on cognitive control, namely on inhibitory control.

Secondary objectives

The secondary objectives of the study are:

1. To assess the efficacy on the evolution of the gambling behavior assessed by the account player-based gambling data, at 6, 14 and 52 weeks.
2. To assess the efficacy on the evolution of the self-reported gambling practice, and of quality of life at 0, 6 and 14 weeks.

3. To assess the efficacy on the evolution of inhibition performance at the neuropsychological level at 0, 6 and 14, weeks.
4. We will also assess the acceptability of this program and the preferred level of guidance of the non-treatment seeking problem gamblers as factor of response.

METHODS AND ANALYSIS

Study design

Our study is a national online research. It is a therapeutic web-based, comparative, randomized controlled trial, 2 arms, single blinding, with 52 weeks follow-up: (1) clinical assessments at baseline, and weeks 6 and 14; (2) gambling account based data extracted from the French online gambling regulation authority (ANJ) at baseline week 6, 14 and 52. The Consolidated Standards of Reporting Trials (CONSORT) flow chart of the trial is depicted in **figure 1**.

Sample selection

Willing gambling service providers regulated by the ANJ and the ANJ will propose a communication on the study on their website to promote the study. The communication will also be promoted in newspapers, radio programs and gamblers online forums. All participants (n=200) will be enrolled in 20 months by an online procedure. Inclusion criteria will be: (1) over 18 years old gamblers, (2) Willing to share his/her first name, last name, exact birthdate, and exact place of birth (city + department). These information are needed to extract ANJ player account-based gambling data, to avoid any doubloon or homonym, (3) Canadian Problem Gambling Index- Problem Gambling Severity Index (CPGI- PGSI)-recent ≥5 (recall period reduced to last month), (4) Affiliated to or beneficiary of the French social security system and resident in France (5). The only Non-inclusion criteria will be (1) Gamblers cannot speak or understand French.

Randomization and group allocation

Randomization will be made via a central web-based system. Treatment (cognitive training or control intervention) will be allocated according to a computer-generated randomization list with a 1:1 ratio, balanced by blocks of variable and undisclosed size.

Screening and obtaining consent

There is no screening visit. Any gambler willing to participate in the study will have to contact the investigator by email. The investigator will send back the information notice to any gamblers contacting him. In the same email, the investigator will ask for emailing back their telephone number in order to perform the inclusion visit by phone.

Patients who have consent and fulfilling all inclusion and exclusion criteria will be included by phone. A medical doctor will call back the gambler to explain the study, and the gambler will be able to ask any question on the study purpose, design, scheduling, intervention, following steps, data collection processes. The person's free and informed oral consent will be obtained by phone the person is enrolled on the study. Inclusion criteria will be checked. The person will specifically confirm his consent by ticking the box indicating that he freely accepts to participate on the online e-clinical register form (e-CRF) (Cleanweb®).

Trial flow

The included gamblers will be informed that they will be called back the same day or in a 3-day period by a neuropsychologist to complete initial assessment (baseline) and to be presented the online data collection process and the training program (corresponding to the randomization group, blinded to the gambler).

Each participant should use online training twice a week at home via internet, for 6 weeks. The advised duration for one online training session is 30 minutes. An optional debriefing by phone is proposed in both groups, up to 15 minutes twice a week. The guidance will follow a semi-structured framework including a focus on the emotion associated with the task completion and a focus on the transferability of the tasks in the patient real life. The neuropsychologist will have access to performances of the subjects through the therapist interface on the training program.

All follow up data collection at T1 6 weeks (+/- 1 week), T2 14 weeks (+/- 2 weeks) will be made by internet. E-mail and SMS reminders will be sent to participants to invite them completing the online assessments at the right time. If no response at all, they could be joined by phone to avoid being classified as lost to follow-up participants.

Account player-based gambling data (last 4 weeks before endpoint, provided by week for each criterion) will be retrospectively extracted from ANJ database 52 weeks after the participant inclusion.

Interventions

Experimental Intervention

The cognitive training is a computerized cognitive training targeting inhibitory control of motor response which has been elaborated in collaboration with a provider of softwares for neuropsychological applications (Scientific Brain Training®). It has been derived by the existing validated program Presco® HappyNeuron by SBT.[32] Two screen captures from the cognitive program can be seen in **figure 2**. The tasks included in the program have been selected and modified to target inhibition and be adapted to the population of gamblers whose executive impairments are less important than those encountered in substance used disorders.[33] More challenging tasks avoid ceiling effect and could thus enhance patients motivation to progress

over the training. Patients must train twice a week for an advised duration of 30-minutes, for six weeks. The tasks are contextualized and gamificated. The names and the instructions for the six tasks are the following:

- “Catch the ladybird”: "click as fast as possible on the ladybird that appears at random on your screen. Here, the challenge is that the more ladybirds you catch, the smaller and faster they become! Multiple challenge levels make this even more fun. You will need to focus on the task at hand and resist any distraction that might arise".
- “Find your way”: "a trail made up of stones will light up at random and you must memorize the path it creates. This exercise requires you to reproduce the itinerary alternatively from the beginning to the end and from the end to the beginning”.
- “Under pressure”: "you have to determine the distance between two objects, by quickly scanning the whole screen, and avoiding a color-like distractor".
- "Gulf Stream": "to click as fast as possible on a target-fish previously memorized and avoid clicking on close distractor-fishes crossing the screen”.
- "Don’t fall in the trap": "to click on target-backboards avoiding close distractor-backboards”.
- "Color and word Stroop task": "In the first trial, the written color name differs from the color ink it is printed in, and the participant must say the written word. In the second trial, the participant must name the ink color instead”.

Twelve predetermined levels will be available for every exercise: from the simplest to the most difficult.

Control intervention

It consists in a sensorial program with a similar format that targeting visual acuity. Two screen captures from the sensorial program can be seen in **figure 3**. This is not a cognitive program *per se* and can be considered as neutral in the addiction field. The following six tasks have been selected in the program “Action Vision”:

- “Recognize a test pattern”: “to locate and to recognize the test pattern and select one of 3 propositions”.
- “Recognize a moving test pattern”: “to locate and to recognize the test pattern before the posting of 3 alternative answers”.
- “Counting of stationary test patterns”: “to count the test pattern before the posting of 3 alternative answers”.

- "Counting of moving targets": "to count moving targets before the posting of 3 alternative answers".
- "Click on the target": "to situate ant to click as fast as possibly on the target".
- "The magnifying glass": "to search with the magnifying glass and to click".

Ten predetermined levels will be available for every exercise: from the simplest to the most difficult.

For both interventions, debriefings calls will be proposed by the neuropsychologist, at the participant convenience. Minimum 0 and maximum 2 15-minutes scheduled appointments a week will be planned.

Measurement instruments

The primary judgement criterion is the change over 6 weeks in the PGSI-recent, a modified version of Problem Gambling Severity Index (PGSI)[34] with a 30 days recall period, self-completed on the e-CRF.

Secondary outcomes will be to assess evolution between baseline (T0), 6 weeks (T1) and 14 weeks (T2) of:

- The short form of the multidimensional impulsivity scale named UPPS-P that assess Urgency, Premeditation, Perseverance, Sensation seeking, and Positive urgency, (UPPS-P Impulsive behavior scale).[35-36]
- TimeLine Follow Back (TLFB) -gambling (money and time including offline gambling).
- EuroQol five dimensions questionnaire (EQ-5D).[37]
- Gambling Quality of Life Scale (GQoLS) (adapted from Alcohol quality of life scale, ongoing study).[38]
- Neuropsychological assessment: Stop Signal Task (SST) measuring cognitive inhibition (Stop signal reaction time criteria).[39]
- We will extracted from the ANJ database (data registered automatically and prospectively) the following account player based gambling data, at baseline (T0), 6 weeks (T1), 14 weeks (T2) and 52 weeks (T3) (last 4 weeks periods): Total Deposit, Total stake by game, Compulsivity (as defined by three consecutive deposits in a 12-hour period of time), Number of deposit in the hour following a stake, Total loss by game, Number of sessions (all games) in a clinical meaning; session is defined as gambling behaviour in itself; we'll consider the beginning of a session when a gambling action occurs after no gambling action since at least 30 minutes,

and the end of the gambling session a gambling action followed by no gambling action during 30 minutes. Session duration (poker only), Gambling time slot (a: 0:00 to 3:59, b: 4:00 to 7:59, c: 8:00 to 11:59, d: 12:00 to 15:59, e: 16:00 to 19:59, f: 20:00 to 23:59). The acceptability of this program will be assessed by the number and the length of training sessions.

-The level of guidance will be assessed by the number and the length of debriefing calls.

Estimating expected effect sizes and required sample size

The sample size was based on the following assumptions on the PGSI: between group change difference: 3 points, estimated standard deviation of the change: 5 points, lost of follow-up at 6 weeks: 55% maximum. With a power of 80%, a two-sided type I error rate of 5%, 200 patients must be included (100 in each group).

Program dropouts

Except for those who withdraw their informed consent, there will be no program dropouts and all participants allocated to either study condition will be included in intention-to-treat (ITT) analyses.

Data analysis

The analysis will include all randomized patients (intention to treat - ITT). Statistical analyses will be performed with SAS software version 9.2 (SAS Institute, Cary, NC). All primary and secondary analyses will also be performed in the modified ITT population, defined as all randomized patients who attend at least one training session. A multiple imputation approach will be used to replace missing values where appropriate for primary and all secondary outcomes. We will create 10 copies of the dataset, with the missing values replaced by imputed values, based on observed data including outcomes and baseline characteristics of participants. Each dataset will be analyzed using standard statistical methods, and the results from each dataset will be pooled into a final result using Rubin's rule.

Analysis of the primary outcome

The change in PGSI-recent total score over 6 weeks will be compared with the student's t-test. If the test application conditions are not met, a Wilcoxon test will be applied.

Analysis of secondary outcomes

The evolution over time of secondary outcomes will be compared with a linear mixed model. Fixed effects introduced in the model will be time, randomization group and interaction between time and randomization group. The need for a model with random intercept and slope (versus random intercept only) will be assessed at the time of the analysis with a likelihood ratio test. An

appropriate modeling of time will be performed if its effect is not linear. The number and the length of training sessions (acceptability) and the number and length of debriefing sessions (level of guidance) will be described in each arm, and compared using t-tests or Wilcoxon tests, as appropriate.

Patient and public involvement

Patient and public were not involved in designing and conducting this research.

Ethics and dissemination

This randomized controlled trial will be executed in compliance with the Helsinki Declaration, and was approved by the CPP (Comité de Protection des Personnes) in October 2017. All professionals will attend a course in Good Clinical Practice (GCP) and get certified by the Groupement Interrégional de Recherche Clinique et d'Innovation d'Île-de-France (public organism providing GCP training).

Current trial status

Recruitment of participants started in February 2019. The last participant is expected to reach the primary endpoint (12-week follow-up) in January 2022. Primary data analysis will begin in March 2022 and the naturalistic follow-up phase of the trial will continue until October 2022 (52 weeks after the last inclusion).

DISCUSSION

No medication is currently approved for the treatment of gambling disorder and prevalence of problem and pathological gambling is increasing[6]. Barriers such as self-stigma have been described as reasons why problem gamblers tend to avoid face to face interventions[7]. Thereby, existing measures and sources of help are not exploited to their full potential. To address this issue, the integration of new technologies in therapeutic settings to develop e-health and online interventions represents an interesting alternative. Online interventions do not require in-person appointments and need a minimum of self-disclosure. It also facilitates access to mental services for populations geographically distant from healthcare facilities and in a context of movement restrictions as it is currently the case during the Covid-19 pandemic. Cognitive training represents a particular good candidate for the online treatment of gambling disorder since it is supposed to target a central dysfunctional process in addiction disorders.[17,24] As a cognitive endophenotype and vulnerability marker, inhibitory control could be trained with durable effects on the behavioral

addiction and any associated mental disorder from a transdiagnostic and dual therapeutic perspective.[28,29,40]

We propose an innovating web-based intervention of cognitive training targeting inhibitory control, with a sensorial program as a comparator to assess its efficacy. A particular caution will be ported to the "launch of study" call, when included participants will be initiated to their attributed program application but also to the data collection platform, and motivated to complete all assessments including neuropsychological ones, in order to avoid missing data. Reminders will help gamblers to complete follow up assessments, and phone calls will be performed in addition to motivate participants in assessment completion if necessary and avoid high attrition rates.

We chose to document efficacy from different perspectives: clinical ones, i.e. subjective patient-reported outcomes and very objective account-based gambling data, and neuropsychological assessments.

Completion of neuropsychological assessments with no face to face is a challenge. A cautious analysis of the whole group will be performed to document parameters of the task in this special setting. We will recommend completing the assessments from a very one computer, with similar conditions of internet access at the three time points.

Guidance has been left to the participant's convenience, learning from our previous findings suggesting possible aversive effect of imposed guidance among problem gamblers participating to a clinical trial with no face to face[31]. If effective, this intervention and its modality without face to face necessity could be a tremendous opportunity to help problem gamblers and reduce treatment gap.

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Contributors AL, AS and AC wrote the first draft of the paper. All authors conceived the study and revised the manuscript for relevant scientific content. All authors approved the final version of the manuscript.

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Competing interests None declared.

Ethics approval This randomized controlled trial will be executed in compliance with the Helsinki Declaration, and was approved by the CPP (Committee for the Protection of Persons) in October 2017.

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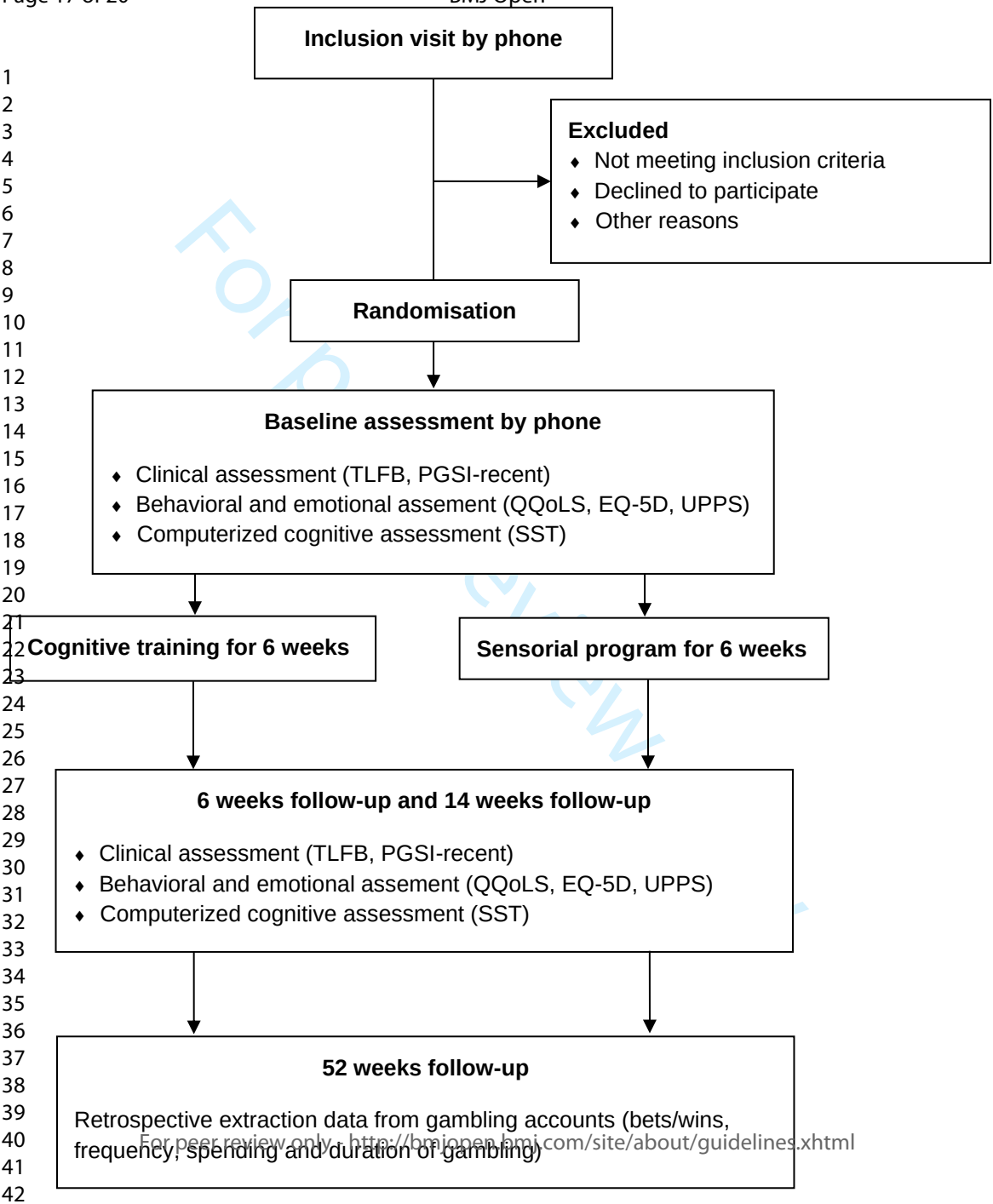
Figure legends

Figure 1. CONSORT-flow diagram summerizes the trial design with the collected measures and time of collection. TLFB, TimeLine Follow Back; PGSI, Problem Gambling Index Severity; GQoLS, Gambling Quality of Life Scale; EQ-5D, EuroQol five dimensions questionnaire; UPPS, multidimensional impulsivity scale; SST, Stop Signal Task; CONSORT, Consolidated Satndards of Reporting Trials.

Figure 2. Figure 2 represents screen captures of two exercises from the active program. The left screen capture is from “Catch the ladybird”; The right screen capture is from “Gulf Stream”. Instructions are described in the experimental intervention section.

Figure 3. Figure 3 represents screen captures of two exercises from the control program. The left screen capture is from “The magnifying glass”; The right screen capture is from “Click on the target”. Instructions are described in the control intervention section.



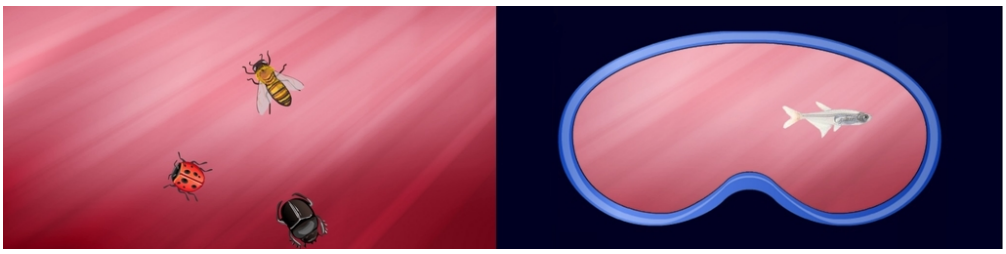


Figure 2 represents screen captures of two exercises from the active program. The left screen capture is from "Catch the ladybird"; The right screen capture is from "Gulf Stream". Instructions are described in the experimental intervention section.

86x21mm (300 x 300 DPI)

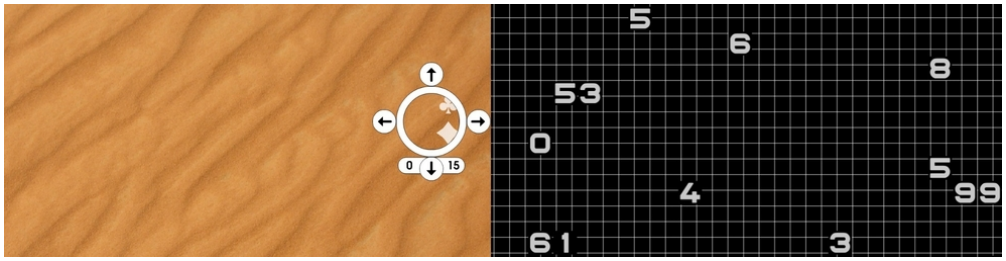


Figure 3 represents screen captures of two exercises from the control program. The left screen capture is from "The magnifying glass"; The right screen capture is from "Click on the target". Instructions are described in the control intervention section.

83x21mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5-6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7-8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	NA
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6-7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6-7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7-8-9-10
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6-7
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	NA
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
Other information			
Registration	23	Registration number and name of trial registry	11
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Study protocol for an online randomized controlled trial among non-treatment seeking problem gamblers: training inhibition in online problem gambling (TRAIN-online) trial.

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Keywords:	Adult psychiatry < PSYCHIATRY, Impulse control disorders < PSYCHIATRY, PUBLIC HEALTH

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Study protocol for an online randomized controlled trial among non-treatment seeking problem gamblers: training inhibition in online problem gambling (TRAIN-online) trial

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Abstract

Introduction Development of fully internet-based programs could provide a new avenue to improve access to healthcare for problem gamblers. In this project, we aim to assess the efficacy of a web-based cognitive intervention targeting inhibitory control among problem gamblers, using a randomized controlled design. As impaired inhibitory control is involved in self-regulation difficulties in behavioral addictions, it represents a particularly relevant cognitive process to target for an online psychological intervention.

Methods and Analysis This will be a single blinded, randomized, comparative therapeutic web-based, controlled trial. Up to 200 non-treatment seeking adult problem gamblers with a Problem Gambling Severity Index-recent (PGSI-recent) score ≥5 will be included. The intervention will be a computerized cognitive training program targeting inhibitory skills. The comparator, an active control, will be a computerized neutral sensorial program. Both programs will be carried out under similar conditions: biweekly online training for 6 weeks and optional telephone support will be offered to patients for debriefing. The main objective of the study is to assess the clinical efficacy of the online cognitive training program at 6 weeks, measured with the PGSI-recent. The secondary objectives are to assess the efficacy on the gambling behavior assessed by the account-based gambling data, on the self-reported gambling practice, and on the inhibition performance at the neuropsychological level at 6, 14 and 52 weeks. We will also assess the acceptability of this program and the preferred level of guidance. Data analysis will be in intention-to-treat.

Ethics and dissemination This RCT will be executed in compliance with the Helsinki Declaration, and was approved by the local ethics boards (CPP) in October 2017. The findings will be published in peer-reviewed journals.

Trial registration number NCT03673800

Strengths and weaknesses of this study:

- This study assesses the clinical efficacy of an innovative web-based intervention of cognitive training in problem gambling.

- Efficacy is documented from different perspectives: clinical ones, i.e. subjective patient-reported outcomes and objective account-based gambling data, and neuropsychological assessments.

- An optional guidance by phone performed by a trained neuropsychologist is proposed and focuses on the transferability of the inhibitory control tasks in the patient's real-life situations related to self-regulation difficulties.

- Completion of an online neuropsychological assessment (using a Stop Signal Task) without face-to-face contact is a challenge and limits the interpretation of the participant's cognitive abilities.

INTRODUCTION

Gambling disorder and gambling-related harms, defined as the adverse impacts from gambling on the health and wellbeing of individuals, families, communities and society[1], represent a major challenge in public health. Despite guidelines for responsible gambling standards[2], the prevalence of gambling disorder is on the rise and was estimated in 2014 at 1.9% of the general French population aged 15 to 75.[3] The most popular gambling games in France are lottery games, far ahead of horse or sports betting, casino and poker. Online gambling affects two million French people, the majority of whom are young men (75.8%), and 45.4% of online gamblers are under 35 years old versus 31% of offline gamblers. The development of online gambling could be linked to the increasing role of the internet and new technologies, particularly during the Covid-19 crisis. Indeed, a recent review showed an increase in online gambling during the pandemic for three groups: younger gamblers, male gamblers and gamblers with higher severity of problem gambling.[4] More generally, online gambling may be more likely to contribute to problem gambling than offline environments.[5]

Despite these alarming data, the treatment gap is concerning: according to the Observatoire Des Jeux (French monitoring center for gambling) national survey[6], only 2% of French problem gamblers seek medical care. Self-stigma and unawareness of professional sources of help have been described as barriers to access the healthcare system in those with gambling disorder.[7] No medication is currently approved for the treatment of gambling disorder. The most established interventions are motivational ones, cognitive behavioral therapies (CBT), or a combination of both techniques, but all have demonstrated limited effect size in published trials.[8,9] Alternative online interventions among the most at-risk online gamblers could enhance the efficacy of the existing strategies and widen the range of existing sources of help.[10] A recent study has shown no between-group difference with placebo of fully online cognitive behavioral therapy among non-treatment seeking problem gamblers.[11] In this project, we will propose an alternative online intervention of cognitive training among problem gamblers.

Cognitive training is a type of cognitive remediation used to improve neuropsychological functioning due to its supposed malleability and its relation to daily activities.[12] Contrary to

CBT, cognitive training targets specific neurocognitive functions, such as attention, memory or executive functions, rather than cognitive distortions. Cognitive training is currently used in several neuropsychiatric conditions and several studies have supported the possibility of generalization of trained skills to daily life activities.[13–17] However, very few cognitive training programs have been published and tested in addictive disorders.[18] Content of assessed programs was heterogeneous, and usually targeted multiple executive functions: attention, working memory and spatial orientation[19–21], visual-motor coordination, and visual-spatial skills.[22] Most of them reported direct neuropsychological outcomes, while some showed parallel evolution in non-strictly cognitive outcomes, i.e. well-being and craving.[21–23]

Volkow and Morales (2015) demonstrated the therapeutic potential in addiction, including gambling disorder, of cognitive training that targets and improves self-regulation skills.[24] The most explored interventions are cognitive bias modification and cue-specific motor response inhibition[25], which are considered specific tasks using addiction-related stimuli. However, Noel et al. (2013) showed a significant effect of non-specific inhibition tasks on decision-making in patients with alcohol use disorder and problem gamblers.[26] Thus, training on tasks unrelated to any substance or addictive behavior should lead to both improvement of the addiction itself and better transferability of the enhanced skills to other behaviors and contexts as they are not limited by addiction-related stimuli but target general and transdiagnostic psychological processes.[27] In a recent study, Penolazzi et al. (2020) tested the transdiagnostic hypothesis of inhibitory control deficits in gambling disorders.[28] The results show preserved memory inhibition and impaired motor response inhibition, a pattern of deficits opposite to that previously reported for substance used disorders. These findings suggest that cognitive training targeting motor and visuospatial inhibitory control could be more adapted to online gamblers.

Fully internet-based randomized controlled trial targeting inhibitory control is an emerging design that could be particularly relevant and acceptable in problem gamblers, for whom the internet is the medium of addictive behavior.[29] We propose a web-based, randomized, controlled, single-blinded clinical trial, assessing the efficacy of a cognitive training program targeting inhibition, in gamblers older than 18 years old and with a Problem Gambling Severity Index-recent (PGSI) ≥5.

Aims and objectives

Primary objective

The main objective of the study is to assess the clinical efficacy of an online computerized cognitive training program targeted on cognitive control, namely on inhibitory control.

Secondary objectives

The secondary objectives of the study are:

1. To assess the efficacy on the evolution of the gambling behavior assessed by the account player-based gambling data, at 6, 14 and 52 weeks from baseline. Gambling behavior includes: total deposit, compulsivity (defined three consecutive deposits within 12 hours), number of deposit in the hour following the stake, total loss per game, number of sessions (a session is defined as a gambling behavior where the beginning of a session starts when a gambling action occurs after no gambling action for at least 30 minutes, and the end of the session is a gambling action followed by no gambling action for 30 minutes), session duration and gambling time slot.
2. To assess the efficacy on the evolution of the self-reported gambling practice, and of quality of life at 6 and 14 weeks from baseline.
3. To assess the efficacy on the evolution of inhibition performance at the neuropsychological level at 6 and 14 weeks from baseline.
4. We will also assess the acceptability of this program and the preferred level of guidance of the non-treatment seeking problem gamblers according to participation in training sessions.

METHODS AND ANALYSIS

Study design

Our study is a therapeutic web-based, comparative, randomized controlled trial, 2 arms, single blinded, with 52 weeks of follow-up. Data will be collected from clinical assessments at baseline, and weeks 6 and 14, and gambling account based data extracted from the French online gambling regulation authority (ANJ) at baseline, week 6, 14 and 52. The ANJ is the regulatory authority supervising online gambling in France. It approves and controls all online gambling games and stores the player account data of all online gaming operators. With participant consent, only player account data from legal online gaming operators (approved by the ANJ) will be extracted. Participants who do not have a player account from an approved gaming operator will be included in the study, but no player account data will be extracted for them. The Consolidated Standards of Reporting Trials (CONSORT) flow chart of the trial is depicted in **figure 1**.

Sample selection

Both willing gambling operators regulated by the ANJ as well as the ANJ itself, will publish a communication on their websites to promote the study. The communication will also be promoted in newspapers, radio programs, gambling online forums and online social media platforms (Facebook, LinkedIn, Instagram). All participants (n=200) will be enrolled over 20 months ~~by~~ using an online procedure. Inclusion criteria will be: (1) over 18 years old gamblers, (2) Willing to

share his/her first name, last name, exact birthdate, and exact place of birth (city + department). This information is needed to extract ANJ player account-based gambling data, to avoid any doubloon or homonym, (3) Canadian Problem Gambling Index- Problem Gambling Severity Index (CPGI- PGSI)-recent ≥5 (recall period of one month), (4) Affiliated to or beneficiary of the French social security system, and (5) resident in France. The only non-inclusion criterion will be gamblers who cannot speak or understand French.

Randomization and group allocation

A single-blind randomization will be made by a medical doctor investigator via a central web-based system called Cleanweb®. Cleanweb® is a secure web-based system used for randomization and research data storing. Research data, including adverse events, is thus stored in an electronic Case report Form (e-CRF). Treatment (cognitive training or control intervention) will be allocated according to a computer-generated randomization list with a 1:1 ratio, using blocks of random size. Only the investigators know which participants are in the cognitive training or control intervention group.

Screening and obtaining consent

There is no screening visit. Any gambler willing to participate in the study will have to contact the medical doctor investigator by email, who will send back the information notice. In the same email, the investigator will request their telephone number in order to perform the inclusion visit by phone.

Consent will be obtained in a two-step process: an oral consent by phone and an online confirmation in the web-based system Cleanweb®. After being given all the relevant study information (study purpose, design, scheduling, intervention, following steps, data collection processes) the person's free and informed oral consent will be obtained by the medical doctor during the inclusion visit by phone. Then, if the inclusion and exclusion criteria are fulfilled, the person will be called back within three days by a neuropsychologist investigator to complete the initial assessment (baseline) in Cleanweb®. Prior to completing the questionnaires in Cleanweb®, the participant will confirm their consent by ticking a box indicating that they freely accept to participate.

Trial flow

In a first call, a medical doctor will inform the participant about the study, collect consent, check for inclusion and exclusion criteria and the randomization. Next, a neuropsychologist will call (within three days) the participant to present the online data collection process. For data collection, a link will be sent by email to the participant to complete the online questionnaires. The link will only allow the participant to confirm or not their consent, complete the questionnaires

and store the data. It will not give access to other information about the study such as the randomization group. After completing all questionnaires, the participant will be presented with the training program corresponding to randomization group (blinded).

Each participant should use the online training twice a week at home via internet, for 6 weeks. The recommended duration for one online training session is 30 minutes. An optional debriefing by phone is proposed in both groups, up to 15 minutes twice a week. The guidance will follow a semi-structured framework including a focus on the emotion associated with the task completion and a focus on the transferability of the tasks in the patient's real life. The neuropsychologist will have access to participants' performances through the therapist interface on the training program.

All follow-up data collection at baseline + 6 weeks (+/- 1 week) and baseline + 14 weeks (+/- 2 weeks) will be made by internet. Email and SMS reminders will be sent to participants to invite them to complete the online assessments at the right time. Non-responders will be contacted by phone to avoid being classified as lost to follow-up.

Account player-based gambling data (last 4 weeks before endpoint, provided by week for each criterion) will be retrospectively extracted from the ANJ database 52 weeks after inclusion.

Interventions

Experimental Intervention

The cognitive training is a computerized cognitive training targeting inhibitory control of motor response, developed in collaboration with a software provider for neuropsychological applications (Scientific Brain Training®). It is derived from one of their existing validated programs called "PRESCO".[30] Scientific Brain Training® and Paris University Hospital (AP-HP) are co-owners of this program. There is then no fee to access it. The tasks included in this program have been selected and modified to target inhibition and are adapted to the population of gamblers whose executive impairments are lower than those encountered in substance use disorders.[31] More challenging tasks avoid ceiling effect and could thus enhance patients motivation to progress over the training. The tasks are contextualized and gamified. They are non-specific tasks, which do not have gambling-related stimuli. Indeed, the experimental intervention focuses on the training of the general inhibitory control ability, which is supposed to play a role not only in gambling behaviors but also in other self-regulation difficulties related to daily life. Two screen captures from the cognitive program can be seen in **figure 2**.

A link will be sent by email to the participant to install the software on their computer. The participant will access the cognitive program with a login identifier created by the neuropsychologist. Participants will be able to access the program at any time, but must train twice a week for an advised duration of 30 minutes, for six weeks. During training sessions, the participant will be able to choose one or more tasks to perform. Debriefing calls will be proposed

by the neuropsychologist, according to the participant's wishes. Up to two 15-minute scheduled appointments a week will be planned.

The names and the instructions for the six tasks are the following:

- "Catch the ladybird": "click as fast as possible on the ladybird that appears at random on your screen. Here, the challenge is that the more ladybirds you catch, the smaller and faster they become! Multiple challenge levels make this even more fun. You will need to focus on the task at hand and resist any distraction that might arise".
- "Find your way": "a trail made up of stones will light up at random and you must memorize the path it creates. This exercise requires you to reproduce the itinerary alternatively from the beginning to the end and from the end to the beginning".
- "Under pressure": "you have to determine the distance between two objects, by quickly scanning the whole screen, and avoiding a color-like distractor".
- "Gulf Stream": "to click as fast as possible on a target-fish previously memorized and avoid clicking on close distractor-fishes crossing the screen".
- "Don't fall in the trap": "to click on target-backboards avoiding close distractor-backboards".
- "Color and word Stroop task": "In the first trial, the written color name differs from the color ink it is printed in, and the participant must say the written word. In the second trial, the participant must name the ink color instead".

Twelve predetermined levels will be available for every exercise: from the simplest to the most difficult.

Control intervention

The control intervention consists in a sensorial program with a similar format that targets visual acuity. Two screen captures from the sensorial program can be seen in **figure 3**. This is not a cognitive program *per se* and can be considered as neutral in the addiction field.

Access to the sensorial program as well as the duration and format of the training follow the same procedures as for the experimental group.

The following six tasks have been selected in the program "Action Vision":

- "Recognize a test pattern": "to locate and to recognize the test pattern and select one of 3 propositions".

- "Recognize a moving test pattern": "to locate and to recognize the test pattern before the posting of 3 alternative answers".
- "Counting of stationary test patterns": "to count the test pattern before the posting of 3 alternative answers".
- "Counting of moving targets": "to count moving targets before the posting of 3 alternative answers".
- "Click on the target": "to situate and to click as fast as possibly on the target".
- "The magnifying glass": "to search with the magnifying glass and to click".

Ten predetermined levels will be available for every exercise: from the simplest to the most difficult.

Measurement instruments

The primary outcome measure is the change over 6 weeks in the PGSI-recent, a French translation and modified version of the Problem Gambling Severity Index (PGSI)[32] with a 30-days recall period, self-completed online in Cleanweb®. PGSI has been identified as a tool to measure change in problem gambling.[33] The original scale has a 12-month recall period. This period was shortened to 30 days for our study. The PGSI consists of nine items which are assessed on a four-point scale: never (1), sometimes (2), most of the time (3) almost always (4). The total score ranges from 0 to 27.

Secondary outcomes will be to assess evolution between baseline (T0), 6 weeks (T1) and 14 weeks (T2) of:

- The short form of the multidimensional impulsivity scale named UPPS-P that assesses Urgency, Premeditation, Perseverance, Sensation seeking, and Positive urgency, (UPPS-P Impulsive behavior scale).[34,35]
- TimeLine Follow Back (TLFB) -gambling (money and time including offline gambling).
- EuroQol five dimensions questionnaire (EQ-5D).[36]
- Gambling Quality of Life Scale (GQoLS) (adapted from Alcohol quality of life scale, ongoing study).[37]
- Neuropsychological assessment: Stop Signal Task (SST) measuring cognitive inhibition (stop signal reaction time criteria).[38]
- We will extract from the ANJ database (data collected automatically and prospectively) the following account player based gambling data, at baseline, 6 weeks, 14 weeks and 52 weeks (last 4 weeks): Total Deposit, Total stake per game, Compulsivity (as defined by three

consecutive deposits within 12 hours), Number of deposits in the hour following a stake, Total loss per game, Number of sessions (all games): a session is defined as gambling behaviour, whereby the beginning of a session is defined when a gambling action occurs after no gambling action in at least the last 30 minutes, and the end of the gambling session is a gambling action followed by no gambling action for 30 minutes), Session duration (poker only), Gambling time slot (a: 0:00 to 3:59, b: 4:00 to 7:59, c: 8:00 to 11:59, d: 12:00 to 15:59, e: 16:00 to 19:59, f: 20:00 to 23:59). The acceptability of this program will be assessed by the number and length of training sessions and dropout rate.

- Level of guidance will be assessed by the number and length of debriefing calls. We assume that number and length of calls represent intensity criteria and are considered as a change factor.

Estimating expected effect sizes and required sample size

The sample size was based on the following assumptions on the PGSI: between group change difference: 3 points, estimated standard deviation of the change: 5 points, loss to follow-up at 6 weeks: 55% maximum. With a power of 80%, a two-sided type I error rate of 5%, 200 patients must be included (100 in each group).

Program dropouts

Anticipated 55% maximum for loss to follow-up at 6 weeks. Except for those who withdraw their informed consent, all participants allocated to either study condition will be included in intention-to-treat (ITT) analyses.

Data analysis

The analysis will include all randomized patients (ITT population). Statistical analyses will be performed with SAS software version 9.2 (SAS Institute, Cary, NC). All primary and secondary analyses will also be performed in the modified ITT population, defined as all randomized patients who attend at least one training session. A multiple imputation approach will be used to replace missing values where appropriate for primary and all secondary outcomes. We will create 10 copies of the dataset, with the missing values replaced by imputed values, based on observed data including outcomes and baseline characteristics of participants. Each dataset will be analyzed using standard statistical methods, and the results from each dataset will be pooled into a final result using Rubin's rule.

Analysis of the primary outcome

The change in PGSI-recent total score over 6 weeks will be compared with the student's t-test. A Wilcoxon test will be applied if data are non-normally distributed.

Analysis of secondary outcomes

The evolution over time of secondary outcomes will be compared with a linear mixed model. Fixed effects introduced in the model will be time, randomization group and interaction between time and randomization group. The need for a model with random intercept and slope (versus random intercept only) will be assessed at the time of the analysis with a likelihood ratio test. An appropriate modeling of time will be performed if its effect is not linear. According to Sekhon et al. (2017), 'if an intervention is considered acceptable, patients are more likely to adhere to treatment recommendations and to benefit from improved clinical outcomes'.[39] Thus, we consider the number and the length of training sessions and dropout rate as proxies for acceptability. Indeed, we assume that if the patient perceived the program as effective, he would implant the intervention in his daily life. According to Simons and Kursawe (2019), feasibility is 'the proportion of patients who were offered treatment who completed and the number of sessions attended'.[40] Thus, we will use the number of training sessions and the number of debriefing calls as a measure of feasibility. The number and the length of training sessions, the dropout rate and the number of debriefing calls will be described in each arm, and compared using t-tests or Wilcoxon tests, if data are non-normally distributed.

Patient and public involvement

Patients were not involved in designing and conducting this research. The French online gambling regulation authority (ANJ) and the willing gaming operators regulated by it are involved in the recruitment process by sharing a communication about the study on their websites. They also share player account data collected during the study (up to 52 weeks after inclusion). Scientific Brain Training® provides the experimental and control programs (which have been adapted for the study) and the software associated.

Monitoring

The sponsor (AP-HP, Clinical Research and Innovation Department) will monitor the study with a frequency depending on inclusion rates: two or three times a year.

Ethics and dissemination

This randomized controlled trial will be executed in compliance with the Helsinki Declaration, and was approved by the local ethics board (CPP, Comité de Protection des Personnes) in October 2017. All professionals will attend a course in Good Clinical Practice (GCP) and get certified by the Groupement Interrégional de Recherche Clinique et d'Innovation d'Île-de-France (public organism providing GCP training). The findings will be published in peer-reviewed journals.

Current trial status

Recruitment of participants started in February 2019. The last participant is expected to reach the primary endpoint (12-week follow-up) in January 2022. Primary data analysis will begin in March 2022 and the naturalistic follow-up phase of the trial will continue until October 2022 (52 weeks after the last inclusion).

DISCUSSION

In this article, we describe the protocol of our innovative web-based intervention of cognitive training targeting inhibitory control, with a sensorial program as a comparator to assess its efficacy. The integration of new technologies in therapeutic settings to develop e-health and online interventions represents an interesting alternative to classical psychological interventions. Indeed, although classical interventions such as cognitive and behavioral therapy have been shown to be effective in treating gambling disorder, gamblers make little use of these services.[41–44] Inhibitory control training is an emerging intervention focusing on a psychological process known to be impaired in different psychiatric conditions.[28] Thus, as a cognitive endophenotype and vulnerability marker, inhibitory control could be trained with durable effects on behavioral addiction and any associated mental disorder from a transdiagnostic and dual therapeutic perspective.[27,28,45] Moreover, our program could facilitate access to mental services for populations geographically distant from healthcare facilities or living in a context of movement restrictions, as it is currently the case during the Covid-19 pandemic.

Despite these benefits, some risks and limitations must be considered for our online study. Particular care will be taken during the first calls, when included participants will be initiated to their attributed program application, to the data collection platform, and motivated to complete all assessments including neuropsychological ones. To prevent high dropout rates and non-compliance issues, automatic reminders will help gamblers to complete follow-up assessments, and phone calls will be made to motivate participants in assessment completion if necessary. Guidance will be available according to the participant's wishes, learning from our previous findings suggesting possible adverse effects of imposed guidance among problem gamblers participating in an online clinical trial.[11] Moreover, completion of neuropsychological assessments without face-to-face contact is a challenge. A cautious analysis of the whole group

will be performed to document parameters of the task in this special setting. We will recommend completing the assessments from the same computer, with similar conditions of internet access at the three time points. Another limitation is that we cannot know why some participants refuse the debriefings. We will therefore be cautious about the conclusions drawn from the statistical analyses of guidance. We will also take into consideration the influence of Covid-19 pandemic on gambling behavior[4] with secondary analyses of the socio-demographic and gambling characteristics of gamblers included during the lockdowns in France.

If summary, this intervention and its modality without requirement for face-to-face contact could be a tremendous opportunity to help problem gamblers and reduce the treatment gap.

Contributors AS, AC, RM, CL, YL, AB, PP and AL were involved in conception and trial design. AL, AS and AC wrote the first draft of the paper and revised the manuscript for relevant scientific content. All authors approved the final version of the manuscript. AL provided statistical expertise. All authors are or will be involved in acquisition, analysis and interpretation of data.

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Competing interests None declared.

Ethics approval This randomized controlled trial will be executed in compliance with the Helsinki Declaration, and was approved by the CPP (Committee for the Protection of Persons) in October 2017.

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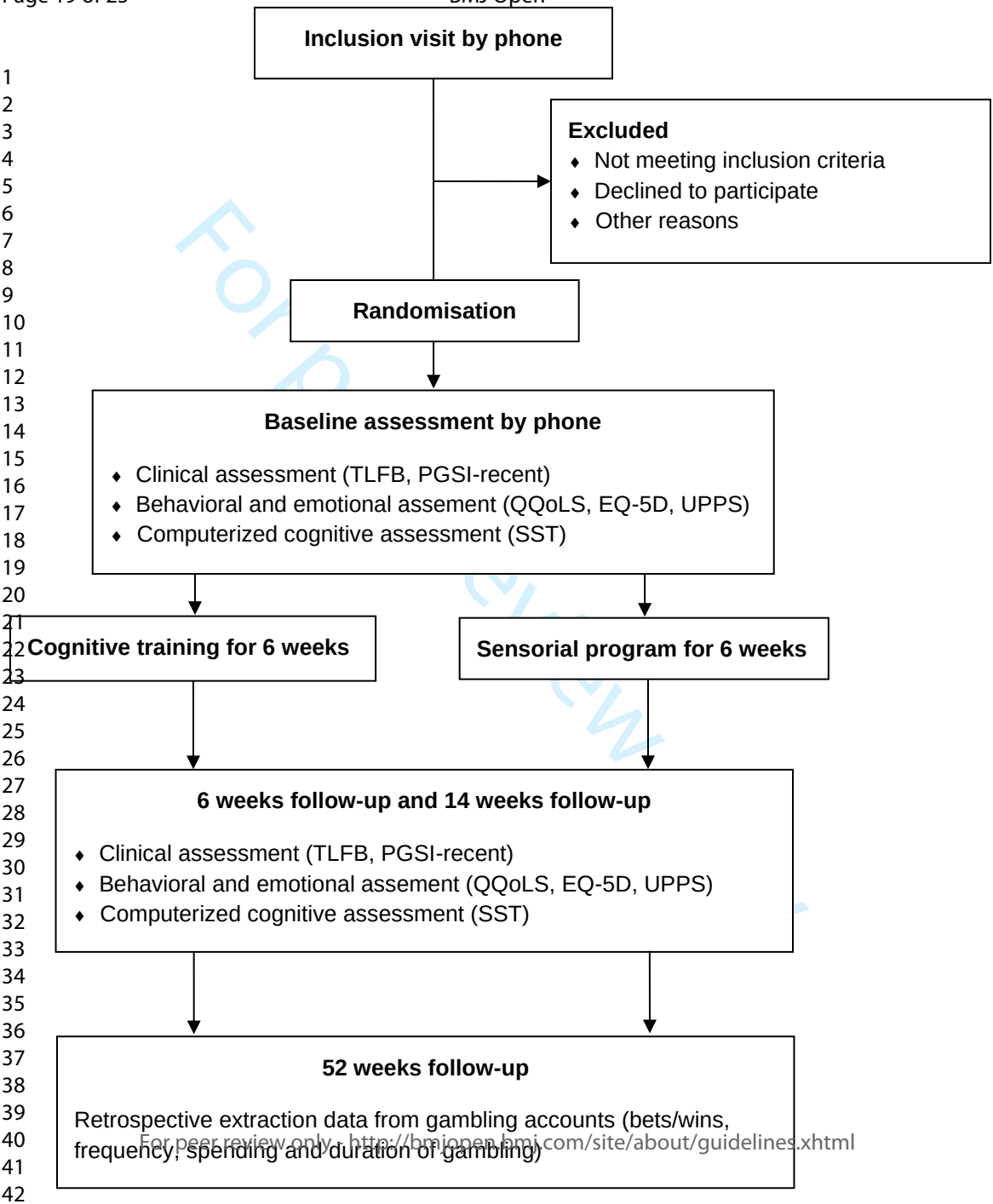
Figure legends

Figure 1. CONSORT-flow diagram summarizing the trial design with the collected measures and time of collection. TLFB, TimeLine Follow Back; PGSI, Problem Gambling Index Severity; GQoLS, Gambling Quality of Life Scale; EQ-5D, EuroQol five dimensions questionnaire; UPPS, multidimensional impulsivity scale; SST, Stop Signal Task; CONSORT, Consolidated Standards of Reporting Trials.

Figure 2. Figure 2 represents screen captures of two exercises from the active program. The left screen capture is from “Catch the ladybird”; The right screen capture is from “Gulf Stream”. Instructions are described in the experimental intervention section.

Figure 3. Figure 3 represents screen captures of two exercises from the control program. The left screen capture is from “The magnifying glass”; The right screen capture is from “Click on the target”. Instructions are described in the control intervention section.



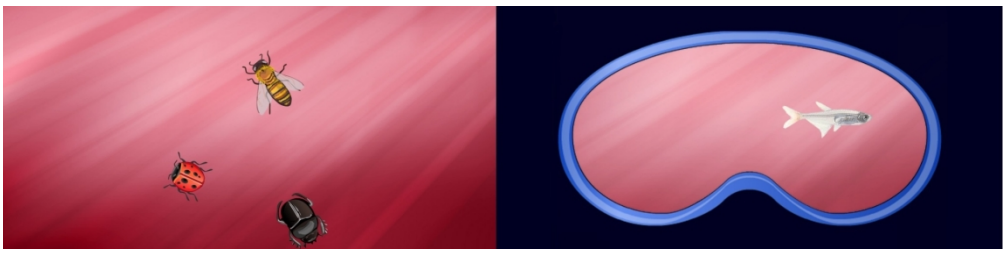


Figure 2 represents screen captures of two exercises from the active program. The left screen capture is from "Catch the ladybird"; The right screen capture is from "Gulf Stream". Instructions are described in the experimental intervention section.

86x21mm (600 x 600 DPI)

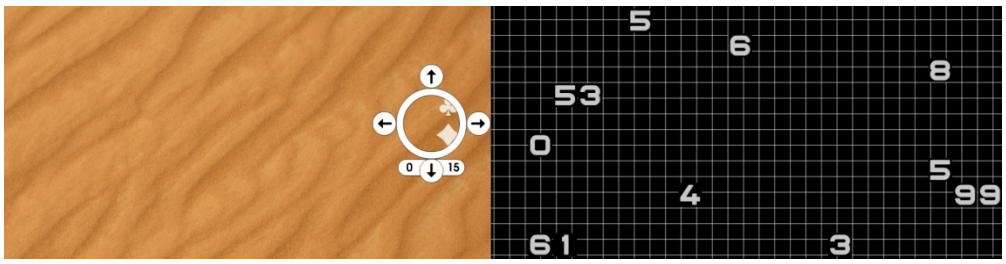


Figure 3 represents screen captures of two exercises from the control program. The left screen capture is from "The magnifying glass"; The right screen capture is from "Click on the target". Instructions are described in the control intervention section.

83x21mm (600 x 600 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	17-18
Protocol version	3	Date and version identifier	18
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_2-3_____
	6b	Explanation for choice of comparators	__4____
Objectives	7	Specific objectives or hypotheses	_4-5_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___5___
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___5-6-7_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__6_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__7-8-9_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__6-7_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_10_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_9-10_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__6-7_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_5-6_____

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__10-11_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____6_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____6_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____6_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___NA_____

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_9-10_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_10-11_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__6_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_10-11_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__NA_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___10-11_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____11_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__NA_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__6___
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_11_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_NA_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_6-7_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6-7_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_11_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	19_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.